# SELECTED HIGHLIGHTS IN IMMUNOLOGICAL RESEARCH IN THE LAST DECADE

Michael SELA

*Department of Chemical Immunology,*
*The Weizmann Institute of Science, Rehovot, Israel*

Received 1 February 1974

This is an impressionistic and, therefore, undoubtedly subjective view of one immunologist on what seem to him the most interesting developments in the broad realm of immunology in the last ten years. Even to mention exclusively the titles of all those studies which deserve comment here would take up more than all the space allotted. I must thus start by pleading with all those friends and colleagues whose interesting work is not mentioned here to bear with me.

The progress of immunology on the molecular level has been enormous, and it is not an exaggeration to state that the basic structure of antibody has been essentially formulated and solved within this decade. This success was symbolized in the joint award of the Nobel prize in Medicine and Physiology for 1972 to Rodney Porter [1] and Gerald Edelman [2]. On the antigen side, we have reached a much better understanding of the molecular basis of antigenicity (and of other immunological phenomena) largely due to the use of precisely designed immunogens. The synthetic approach has also been instrumental in the recent developments concerned with the genetic control of immune response.

Lately we have begun to understand immunology at a cellular level. Certain crucial questions are still a matter of deep controversy, and the molecular approach to cellular immunological phenomena has not been yet used too extensively.

## 1. The antibody story

Papain cleavage of immunoglobulin G (IgG) [3] resulted in two Fab fragments, possessing the sites binding the antigen, and one Fc fragment (easily crystallizable), possessing several other biological properties such as the capacity to fix complement and to bind to cells. On the other hand, Edelman [4] showed that IgG is a multichain structure. This led to the four chain – two H (heavy) and two L (light) – model of IgG (5) (fig. 1). This model immediately provided the molecular basis for the genetic markers of immunoglobulins known as allotypes [6,7]. It also became apparent at an early stage that light and heavy chains are present in all classes, and thus that all immunoglobulins have fundamentally the same structure [8].

Antibodies are very heterogeneous, but homogeneous immuglobulins with antibody activity have been described and characterized in detail in the last decade. They were first of all identified among the paraproteins of patients with Waldenström's macroglobulinemia and multiple myeloma. A Waldenström macroglobulin was shown to be an antibody of the IgM class directed against human IgG [9]. Human and mouse myeloma proteins, mostly of the IgA class, were described possessing specificities as disparate as for the dinitrophenyl group and phosphorylcholine [10–12]. Their homogeneity led to a better understanding of structure and specificity than had been possible with heterogeneous antibodies. Homogeneous antibodies have also been obtained experimentally. Thus, antibodies with specificity directed to streptococcal [13] and pneumococcal [14] polysaccharides were found to be monoclonal. Repeated pasages of a very small number of cells also caused production of antibodies of very limited heterogeneity [15], and so did antibody production by microcultures vitro [16].

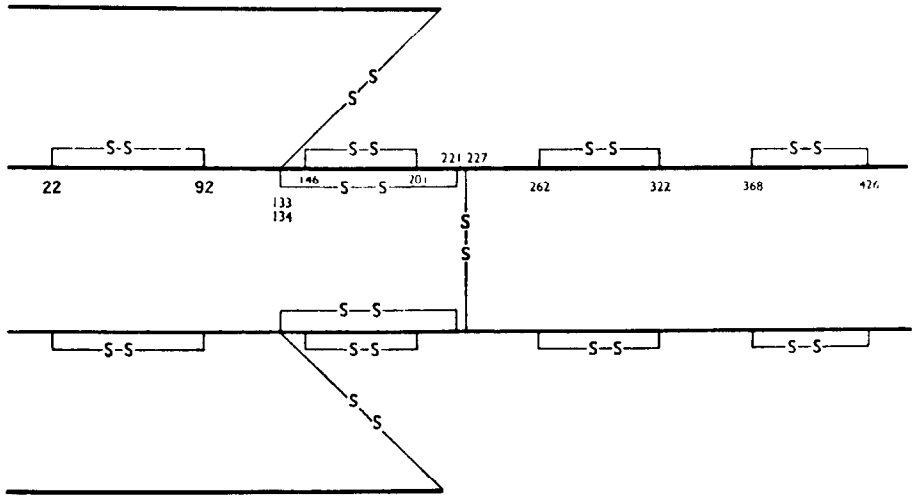


Fig. 1. The structure of rabbit IgG. The rather complex arrangement of inter- and intrachain disulfide bonds in the heavy chain is shown. From Porter [1].

That antibodies of different specificities have distinctive amino acid compositions [17], and that antibody fragments [18,19] or entire molecules [20] could be completely unfolded reversibly, showed that antibody specificity was encoded in the amino acid sequence exclusively. The elucidation of the first amino acid sequences of the light chain [21,22] led to the conclusion that these chains are made of a variable (V) and a constant (C) portion, and thus that two genes code for each immunoglobulin light chain [23]. Similarly, the heavy chain of IgG ($\gamma$ chain) is composed of one variable and, in this case, three constant regions [24, 25]. These studies culminated in the elucidation of the complete amino acid sequence of an IgG molecule [26], followed in the last year by the complete amino acid sequence of the pentameric IgM molecule [27].

The progress in the research of the antibody molecule has been reflected in several symposia [28–32], review articles [33–36] and in the volume published on the occasion of the First International Congress of Immunology [37]. One may find there in detail the convincing case made for the two extreme types of theories of antibody formation: germ line theories, which assume that all the information, i.e. antibody genes, may pre-exist in the germ line; and somatic theories, which assume that antibody diversity is generated during somatic differentiation (mutation or recombination) (for literature see, e.g., Williamson [38]).

Singer and Thorpe [38a] and Edelman and his colleagues [2] suggested that the IgG molecule is folded in a series of compact domains, each formed by separate V homology regions or C homology regions (fig. 2). In such an arrangement, each domain is stabilized by a single intrachain disulfide bond and is linked to neighboring domains by less tightly folded stretches of the polypeptide chains. Do changes occur within the antibody molecule upon reaction with antigen or hapten? And if so, are they limited to the combining site region? Many techniques failed to

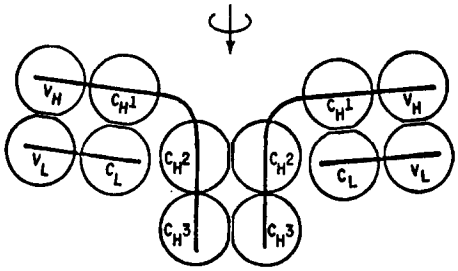


Fig. 2. The domain hypothesis. Diagrammatic arrangement of domains in the free IgG molecule is shown. The arrow refers to a dyad axis of symmetry. Homology regions that constitute each domain are indicated: $V_L$ and $V_H$ are domains made up of variable homology regions; $C_L$, $C_H1$, $C_H2$ and $C_H3$ are domains made up of constant homology regions. Within each of these groups, domains are assumed to have similar three-dimensional structures, and each is assumed to contribute to an active site. The V domain sites contribute to antigen recognition functions and the C domain sites to effector functions. From Edelman [2].

detect such changes, while others suggested changes within the combining site [39,39a]. Metzger concluded that no convincing evidence is at hand which demonstrates that reactions at the combining sites of an antibody produce defined conformational changes elsewhere in the molecule [39]. Differences in the circular dichroism spectra of anti-pneumococcal antibodies with a specific hexasaccharide [40] could be interpreted as due either to conformational changes in the combining site of the antibody or to a change in the environment of chromophores within the combining site. Tumerman et al. [41] concluded that flexibility of an antibody decreases upon reaction with hapten. Liberti et al. [42] assumed gross conformational changes within the antibody to explain the change in its tritium exchange properties upon reaction with a synthetic macromolecular antigen. Reaction of antibodies with a tetra-D-alanine hapten led to a large volume contraction, due to a change in conformation upon interaction [43].

Estimation of the size and nature of the combining sites has been reported for several antibodies, including those directed against oligosaccharides [44] and peptides [45,46]. A 'dynamic mapping' of the combining site of a myeloma protein with anti-dinitrophenyl activity was obtained through kinetic studies using relaxation spectrometry [47]. The capacity to bind the antigen specifically is obviously confined to the variable domains of the molecule. So are the idiotypes [48], or the individual antigenic specificities of immunoglobulins [49,50]. The notion of idiotypy of antibodies was first described in 1963 [51].

Considerable progress in the characterization of the active sites of antibodies was achieved by covalent affinity labeling, introduced by Singer [52,53]. Upon inspection of the amino acid sequences of the variable regions of heavy and light chains of immunoglobulin molecules, it became apparent that the positions at which variation occurs are dispersed throughout the variable regions. Certain portions showed a remarkable high degree of variability relative to the background [54]. Three hypervariable regions were found in the light chains [55,55a]. Affinity-labelling techniques using different reagents have labelled residues in each hypervariable region, and labelled residues have never been found far from the hypervariable region [56–59]. The use of affinity labeling reagents with varied distances between the hapten and the 'hook' [60], with two 'hooks' in the same molecule, for cross-linking [61], as well as the use of photoaffinity labeling [62,63], contributed importantly to our knowledge of the antibody combining site.

Active fragments of antibodies, containing the $V_H$, $C_H1$, $V_L$ and $C_L$ domains, have been obtained with papain [1,3], pepsin [64] and other proteolytic enzymes, as well as by limited chemical cleavage with cyanogen bromide [65]. The only successful attempt to obtain a much smaller fully active antibody fragment has been the isolation of a peptic digestion product of an IgA mouse myeloma protein [66]. This fragment, named $F_V$, is formed from the amino terminal half of Fab, i.e. it is composed exclusively of $V_H$ and $V_L$.

Beside the immunoglobulins of the G and M class (IgG, IgM), our knowledge has progressed much on the IgA class, prominent in secretion [67]. Most experimentally-induced mouse myeloma proteins are of this class [68]. The different classes share the same light chains, but differ in the heavy chains, which are

Fig. 3. Electron micrograph of a single mouse IgM selected from a micrograph by Parkhouse et al. [76]. Details of preparation are given in Parkhouse et al. [76].

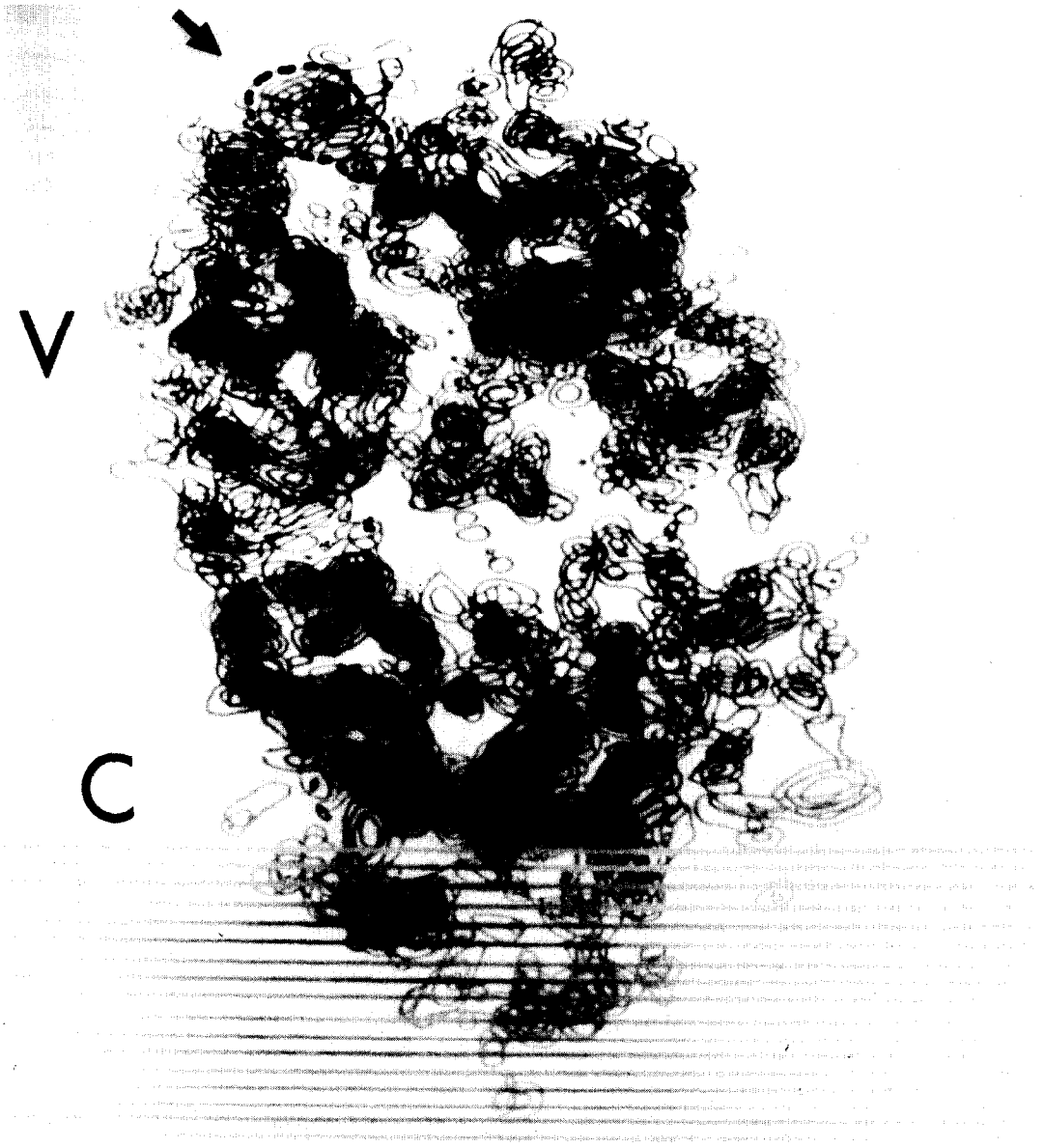


Fig. 4. Photograph of the electron density map of the Fab' fragment of McPC603 protein at 4.5 A resolution. The contours were drawn at equal but arbitrary intervals. Only positive contours above the first are shown. The upper half of the molecule (V) is identified with the variable region and the lower half (C) with the constant region of the fragment. The 2-(5'-acetoxymercury-2'-thienyl)-ethylphosphorylcholine difference peaks in the region believed to be the combining site are enclosed in a heavy dotted line and arrowed. From Padlan et al. [89].

characteristic of the class. One of the most interesting observations in this connection is the discovery of a new chain, denoted J, which is present only in the polymeric IgM and IgA [69]. Two new classes of immunoglobulins have been discovered in recent years: IgD [70,71], and IgE. Reaginic antibodies belong to the latter class [72].

During the last decade we have seen for the first time electron microscopic pictures of IgG [73], IgM [73–76] and IgA [77] molecules. An IgM molecule is illustrated in fig. 3. Electron micrographs have been also obtained of complexes between antibodies and antigens (e.g. [75]) or bifunctional haptens [77,78]. Ultimately, of course, the real 'seeing' is through an X-ray crystallographic study of immunoglobulin molecules, and their active sites. Poljak et al. [79] first investigated an Fc fragment. An intact human IgG myeloma protein has been analyzed at 6 Å resolution [80]. More recently, the structure of a light chain dimer (Bence-Jones protein) at 3.5 Å resolution has been reported [81].

Most recently, the structure of the Fab′ fragment of a human myeloma IgG was determined by X-ray crystallographic analysis at 2.8 Å resolution [82]. No α-helical conformation can be seen in the structure. The overall dimensions of the Fab′ molecule are 80 × 50 × 40 Å. Each of the four homology subunits can be enclosed in a parallelepiped of 40 × 25 × 25 Å. A centrally located cleft divides the molecule into two structural domains, the variable and constant moieties. The structural subunits $C_L$ and $C_H1$ interact over a wider area and are more tightly packed than the $V_L$ and $V_H$ subunits. All four subunits are strikingly similar in their three-dimensional folding, as expected from the homology of their amino acid sequences and in agreement with the proposal of gene duplication as a mechanism of origin of immunoglobulin genes. However, although the $V_L$ and $V_H$ subunits share the basic 'immunoglobulin-fold' of the $C_L$ and $C_H1$ subunits, they include an additional length of polypeptide chain in the form of a loop not present in the constant homology regions. The regions of hypervariable sequences of both L and H chains occur at one end of the molecule and are fully exposed to the solvent. There is no cavity in this region (probably the 'active' site), only a shallow groove. Although the structurally related L and H chains are clearly complementary, it appears that the H-chain exposes a larger area at the 'active' site [82].

In order to obtain reliable information about the combining site of antibody it is necessary to possess crystals with and without the hapten. This has been accomplished for the anti-dinitrophenyl mouse IgA myeloma protein [83], and led the way to the recently reported structure, at 4.5 Å resolution, of a phosphorylcholine-binding Fab (papain-produced) fragment of McPC603 mouse myeloma immunoglobulin [84]. The electron density can be divided into four distinct globular regions which are interpreted to correspond to the four domains in the molecule (fig. 4). The hapten-binding site lies between two domains near one end of the molecule.

## 2. Molecular basis of antigenicity

Following the classical studies of Landsteiner [85], great progress has been made in the investigation of antigenic specificity, making largely use of haptens [46,86,87]. A useful distinction has been made between the notions of immunogenicity (i.e., capacity to trigger an immune response, independently of its specificity) and antigenic specificity [88,89].

With the progress in the determination of structures of proteins and nucleic acids, it is not surprising that great advances have been made in the elucidation of their immunochemical properties [90,91]. Whereas most fibrillar and all denatured globular proteins exhibit exclusively 'sequential' antigenic determinants, native globular proteins possess mainly or uniquely 'conformation-dependent' determinants [92,93]. Myoglobin [94,95], egg white lysozyme [96,97] and staphylococcal nuclease [98] are among the proteins analyzed most thoroughly from this point of view. A nice illustration of the sequential versus conformation-dependent determinants comes from a study showing complete lack of immunological cross-reaction between the native hen egg white lysozyme and bovine lactalbumin systems, but very good cross-reaction between these two proteins, possessing a large extent of amino acid homology, after they were denatured [99]. The use of enzymes as antigens rather than other proteins, offers the advantage that they possess biologic activity that resides in a limited area of the molecule, and antibodies specific towards this or related regions may have an effect on the catalytic activity [100].

A better understanding of the molecular basis of antigenicity, and of manifold immunological phenomena, became possible due to the use of synthetic antigens [93,99,101–103]. The synthetic approach offers the advantage that, once the immunogenicity of one synthetic material has been unequivocally demonstrated, many analogues may be prepared and tested. If the antigen design is known, it is possible, through a study of compounds showing only limited variations in their chemical formulae, to arrive at conclusions concerning the role of various structural features in their antigenic function. Thus, homopolymers of amino acids are very poor immunogens, and the immunogenicity increases with increased variations in composition. While macromolecular substances are more reliably immunogenic, low molecular weight compounds may be immunogenic provided they have the right composition [104]. The presence of electrical charges on a macromolecule is not a minimum requirement for it to be immunogenic [93], but when the antigen is charged an inverse relationship persists between the net electrical charge on the immunogen and that on the antibodies it provokes [105]. In order to elicit antibody, the immunogenically important area must be readily accessible and cannot be hidden in the interior of the molecule [93].

Synthetic antigens may be prepared, leading to antibodies of almost any specificity desired, such as 'classical' haptens, sugars, nucleosides, pyridoxal, folic acid and methotrexate, a phytoestrogen, ferrocene, the glycolipid cytolipin H (for literature, see ref. [93]), as well as brain lipids [106], angiotensin [107], bradykinin [108], glucagon [109], triiodothyronine [110], morphine [111] and prostaglandin A [112]. The size and nature of peptidic sequential determinants has been analyzed in detail by Schechter [113].

Cross-reactive antibodies may induce profound conformational changes in the antigen. Thus, anti-apomyoglobin antibodies give a white precipitate with myoglobin, the heme being extruded during the reaction [114]. As another illustration may serve the dramatic increase in the enzymatic activity of an almost inactive β-galactosidase mutant upon reaction with antibodies against β-galactosidase from wild-type *E. coli* [115]. The conversion of a not yet helical small polymer of Tyr–Ala–Glu into α-helical shape upon reaction with antibodies against a higher molecular weight polymer of the same sequence, which is helical under physiological conditions, was followed by circular dichroic methods, thus showing an induced fit upon the reaction between the active sites of two biologically relevant macromolecules [116]. An acidic synthetic copolymer was shown to possess determinants whose conformation depends on reaction with calcium ions [117].

Synthetic antigens have been described capable of provoking antibodies cross-reacting with a bacterial cell wall [118], with the basic protein of the myelin sheath (such polymers may suppress the experimental disease, allergic encephalomyelitis, ref. [119,120]) as well as with collagen [121]. In the latter case the cross-reaction is due to the similarity in three-dimensional structure. The synthesis of a portion of hen egg white lysozyme, denoted 'loop', followed by its chemical attachment to a branched amino acid polymer, yielded a synthetic immunogen which provoked antibodies reacting with lysozyme through a unique, conformation-dependent region [122]. All the conformational studies, as well as other studies [103], lead to the inevitable conclusion that an antigenic determinant is recognized while the immunogenic macromolecule is still intact.

The feasibility of preparing synthetic antigens that can provide antibodies against complex protein determinants conceptually opens the road to the vaccines of the future [123]. With polysaccharides some success has already been achieved. An artificial colitose-containing antigen stimulated antibodies against certain pathogenic Gram-negative bacteria [124]. More recently, an artificial antigen containing 2-*O*-acetyl-abequose was described [125]. Antibodies made against it agglutinate certain strains of *Salmonella*. In another case, a synthetic antigen was built containing the presumed receptor site of wheat-germ agglutinin ([126], see also [127]). The antibodies cross-reacted with the receptor sites on tumor-cell surfaces. Mice immunized against this antigen rejected five times as many transplanted myeloma tumor cells as are rejected by otherwise identically treated control mice. The antigen acted, therefore, as a 'chemical vaccine against tumor progression'.

Synthetic antigens have also been helpful, i.e., in investigations of antigen metabolism [128], delayed hypersensitivity [129], immunological tolerance

(e.g., [130–132]), antigenic competition [133] and the genetic control of immune response [134,135].

### 3. From molecule to cells

Immunocytes are cells involved in the immune process, i.e. in the triggering and maintenance of the immune response. They are mainly long-lived small mononuclear lymphocytes [136]. Macrophages also play a role in most instances of immune triggering [137–139]. The selection theory [140] in its clonal form [141] demands that cells will have receptors for antigen before they encounter antigens. Such receptors were found on immunocyte membranes, and they were found to be immunoglobulins [142–144]. In accordance with the theory, a very low but significant percentage of immunocytes in a normal cell population is able to bind specifically the antigen [145–147]. Cells have been fractionated on the basis of their receptor for antigen [148–150]. Methods were developed for elegant detection of antibody-producing cells [151] and for antibody synthesis in vitro [152,153], including primary antibody formation in vitro to defined synthetic antigens [154]. It was proven beyond doubt that one cell makes antibodies of only one antigenic specificity (e.g., [155,156]). In agreement with this observation, it was found recently that one cell possesses antigen receptors of only one specificity [157].

The thymus is an organ of paramount importance for the development of immunity [158–160]. The immunocompetent lymphocytes can be divided into two general types on the basis of functional differences: T cells – small lymphocytes that have adapted to certain specific immune functions by virtue of some as yet undefined influence of the thymus (thymus-derived); and B cells – small lymphocytes that have not been directly influenced by the thymus and which are the progenitors of mature antibody-producing cells (see, e.g. [161]). Cooperation between T and B cells has been demonstrated for humoral antibody responses ([162,163], for later literature, see, e.g. [164]). Antigen receptors seem to be present on both types of cells. It is unequivocally established that the receptors on B cells are of immunoglobulin nature (for review, see [39,165]). On the other hand, there is considerable controversy concerning the receptor on the T cell, many reports denying its putative immunoglobulin structure (for review, see [147,161]).

In his brilliant critique of the state of immunological art in 1967 [166], Jerne has discussed, i.e., the 'receptor puzzle'. It is clear that the immunogenic carrier is more than an inert macromolecule to which an antigenic determinant is attached, and that it is crucial in defining both the elicitation and the structure of antibodies [167]. Moreover, it has become clear that in most cases an immune response necessitates the cooperation of two cells whose immunological specificity is different, even though both are capable of reacting with the same immunogen [166,168–171]. This bicellular interaction leading, e.g., to an anti-hapten antibody, is indeed between thymus and bone marrow-derived cells (e.g., [172]). The influence of T cells in the cellular events of induction of antibody formation and tolerance has been summarized recently [173]. Some antigens are 'thymus-independent', most probably because they possess repeating antigenic determinants and are slowly metabolizable (see [164,173]). From a molecular standpoint it is of interest that collagen is a thymus-independent antigen, whereas the gelatin derived from it is thymus-dependent [174]. The thymic function may be replaced by either specific (e.g. [175–177]) or non-specific [178] soluble factors. These seem to differ from the previously described thymic hormones [179,180].

The two types of functionally different lymphocytes may be distinguished by virtue of their surface antigenic markers (for review, see [181]). It was shown recently that antibodies reacting with lymphocyte surface immunoglobulin molecules induce these to gather over one pole of the cell (to 'cap'), suggesting a possible mechanism for lymphocyte triggering by antigen [182]. Many studies have appeared in the last year, extending the initial 'patching' and 'capping' phenomena to other immunocyte markers, which are protein components floating in the lipid bilayer of a cell membrane (e.g., [187]). A suggestion has been made that there are receptors on lymphocytes also for autoantigens, and that it is the autologous serum which inhibits self-recognition [184].

$\beta_2$-Microglobulin is a low-molecular-weight protein constituent of lymphocyte membranes, whose amino acid sequence has been recently determined. It shows

a striking homology with certain parts of immunoglobulin chains [185,186], suggesting for it a possible recognition function. Indeed, it seems that there is a relation between the $\beta_2$-microglobulin, some serologically defined transplantation antigens [187], and recognition units on the T lymphocyte surface, supporting the concept that phenotypic products of the HL-A chromosomal region may function in recognitive processes [188,189].

Progress has been made also in the cell-free biosynthesis of immunoglobulins. Light and heavy chains are made on separate polysomes [190,191]. The biosynthesis of the carbohydrate portion of immunoglobulin chains and their relation to secretion have also been studied [192]. Study of the assembly of immunoglobulin M showed that intracellularly it exists solely in the form of 7 S subunits [193]. Exciting studies are under way on the messenger RNA for light [194–197] and heavy [198] chains. An active antibody has been synthesized in a wheat-germ cell-free system [199].

## 4. Genetic control of immune response

Even though immunity is not inherited, the capacity to respond immunologically well or poorly appears to be under genetic control [134,135,200]. The immune response of guinea pigs to hapten conjugates of poly-L-lysine is predicated upon the presence of an autosomal dominant gene which is referred to as the PLL gene [201]. This finding was followed by the demonstration of a determinant-specific genetic control of antibody formation to a series of branched synthetic polypeptides in inbred strains of mice [202], and by the detection of genetic control at the level of antibody specificity [203]. These studies were performed with synthetic antigens, most probably because their restricted antigenic heterogeneity allowed for clear-cut results. Indeed, when very small doses of complex proteins were used for immunization, genetic differences in response were also detected [204,205]. Direct proof for the hypothesis that the use of complex antigens may blur genetic control of their various unique determinants came from a study of the antigenic determinants of lysozyme [206].

McDevitt and Chinitz have shown that the immune responses of inbred mice to a related series of three branched synthetic polypeptide antigens studied previously [202] are closely correlated with the genotype for the major histocompatibility (H-2) locus [207]. A similar linkage has been observed between the major histocompatibility locus of inbred strain 2 guinea pigs and the PLL gene [208]. Tens of antigens have been by now described, that show clear genetic differences in inbred strains of various animal species, and in many cases these genetic controls are linked to the major histocompatibility locus of the species [209–211]. It has also been reported that specific reaginic antibody response is linked to the HL-A haplotype in humans [212,213].

Genetic control of specific immune responses is now a well-established phenomenon [214], and many responses have been mapped precisely within the H-2 region (e.g., [210]). Thus, e.g., genes for antibody response to IgG and IgA are in independent loci [215]. As the capacity to respond to certain antigens is determined by genes, and some of these lie within the same chromosomal region as the genes for histocompatibility antigens, it seems possible that the products of these genes may themselves be histocompatibility antigens, and that they serve as recognition sites on certain cells (possibly T cells) of the immune system [209,214]. Some indirect evidence supporting the hypothesis that the histocompatibility-linked immune response genes are expressed always on the T cell has been reported recently [214,216,217]. A cellular analysis of several immune response gene systems [135,218–221] led Sela and his colleagues to the conclusion that the genetic defect in the immune response is reflected in thymocytes when the poor response is at the carrier level, whereas it is expressed in the bone marrow population when the low responsiveness is strictly at the determinant level [103].

## 5. Immunology as a tool

Immunological techniques have been used for a long time in other disciplines, but the last decade has seen an exponential increase in the use of immunological tools in literally tens of other fields, for detection of various compounds, for visualization by means of immunofluorescent and radioactive techni-

ques, for isolation of antigens and haptens. It includes studies such as X-ray diffraction of muscle labelled with antibody to C-protein [222], and blocking of the electrophysiological response of the electroplax to carbamylcholine by means of rabbit antiserum against purified *Electrophorus electricus* acetylcholine receptor [223]. I shall mention here explicitly only their diagnostic value.

Antibodies have been used widely for sensitive detection and quantitation of antigens and haptens. These may include small molecules such as drugs and vitamins and macromolecules such as proteins (e.g. hormones, carcinoembryonic antigens) and nucleic acids. The most widely used technique is the radioimmunoassay [224–226]. More recently, both viroimmunoassay (making use of chemically modified bacteriophage) [227–229] and enzymoimmunoassay [230–232a] have been efficiently employed. A modification of the radioimmunoassay extends its use to detection and quantitation of reaginic antibodies [233], and thus opens the road to efficient in vitro diagnosis of allergic diseases.

## 6. Concluding remarks

This summary statement dealt only with antibodies, antigens, cellular cooperation and genetic control of immune response, and even in these fields the list of inevitable omissions is long. Whole fields of immunology, such as autoimmune diseases, immune disorders in man, manipulation of the immune response [37,234], transplantation [235], complement [37,236,237] and tumor immunology [37], have not been mentioned at all.

As for Jerne's 'Waiting for the End' [166], it seems that indeed the end – the solution – is in sight for the antibody molecule. The stage is now set, and the game can start with the cells.

## Acknowledgements

This article was written while the author was a Fogarty Scholar-in-Residence at the Fogarty International Center, National Institutes of Health, Bethesda, Maryland. I would like to thank Dr. Henry Metzger for helpful discussions.

## References

[1] Porter, R.R. (1973) Science 180, 713.
[2] Edelman, G.M. (1973) Science 180, 830.
[3] Porter, R.R. (1959) Biochem. J. 73, 119.
[4] Edelman, G.M. (1959) J. Amer. Chem. Soc. 81, 3155.
[5] Porter, R.R. (1962) Basic Problems in Neoplastic Disease (Gellhorn, A. and Hirschberg, E., eds.), p. 177, Columbia University Press, New York.
[6] Oudin, J. (1956) Compt. Rend. 242, 2606.
[7] Mage, R., Lieberman, R., Potter, M. and Terry, W.D. (1973) The Antigens (Sela, M., ed.), Vol. 1, p. 299, Academic Press, New York.
[8] Cohen, S. (1963) Nature 197, 253.
[9] Metzger, H. (1967) Proc. Natl. Acad. Sci. U.S. 57, 1490.
[10] Eisen, H.N., Little, R.J., Osterland, C.K. and Simms, E.S. (1967) Cold Spring Harbor Symp. Quant. Biol. 32, 75.
[11] Eisen, H.N., Simms, E.S. and Potter, M. (1968) Biochemistry 7, 4126.
[12] Leon, M.A. and Young, N.M. (1971) 10, 1424.
[13] Krause, R.M. (1970) Federation Proc. 29, 59.
[14] Haber, E. (1970) Federation Proc. 29, 66.
[15] Askonas, B.A., Williamson, A.R. and Wright, B.E.G. (1970) Proc. Natl. Acad. Sci. U.S. 67, 1389.
[16] Luzzati, A.L., Lefkovits, T. and Pernis, B. (1973) Eur. J. Immunol. 3, 636.
[17] Koshland, M.E. and Engelberger, F.M. (1963) Proc. Natl. Acad. Sci. U.S. 50, 61.
[18] Haber, E. (1964) Proc. Natl. Acad. Sci. U.S. 52, 1099.
[19] Whitney, P.L. and Tanford, C. (1965) Proc. Natl. Acad. Sci. U.S. 53, 524.
[20] Freedman, M.H. and Sela, M. (1966) J. Biol. Chem. 241, 5225.
[21] Hilschmann, N. and Craig, L.C. (1965) Proc. Natl. Acad. Sci. U.S. 53, 1403.
[22] Titani, K., Whitley, Jr., E., Avogardo, L. and Putman, F.W. (1965) Science 149, 1090.
[23] Dreyer, W.J. and Bennett, J.C. (1965) Proc. Natl. Acad. Sci. U.S. 54, 864.
[24] Press, E.M. and Hogg, N.M. (1969) Nature 223, 807.
[25] Cunningham, B.A., Pflumm, M.N., Rutishauser, N. and Edelman, G.M. (1969) Proc. Natl. Acad. Sci. U.S. 64, 997.
[26] Edelman, G.M. (1970) Biochemistry 9, 3197.
[27] Putnam, F.W., Florent, G., Paul, C., Shinoda, T. and Shimizu, A. (1973) Science 182, 287.
[28] Porter, R.R., ed. (1966) Proc. Roy. Soc. B, Vol. 166.
[29] Frisch, L., ed. (1967) Cold Spring Harbor Symp. Quant. Biol., Vol. 32.
[30] Killander, J., ed. (1967) Gamma Globulins, Nobel Symposium 3, Almqvist and Wiksell, Stockholm.
[31] Chase, M.W., and Kuhns, W.J., eds. (1970) Ann. N.Y. Acad. Sci., Vol. 169.
[32] Kochwa, S. and Kunkel, H.G., eds. (1971) Ann. N.Y. Acad. Sci., Vol. 190.

[33] Edelman, G.M. and Gall, W.E. (1969) Ann. Rev. Biochem. 38, 415.
[34] Gally, J.A. and Edelman, G.M. (1972) Ann. Rev. Genet. 6, 1.
[35] Hood, L. and Prahl, J. (1971) Adv. Immunol. 14, 291.
[36] Gally, J.A. (1973) The Antigens (Sela, M., ed.), Vol. 1, p. 161, Academic Press, New York.
[37] Amos, D.B., ed. (1971) Progress in Immunology, Academic Press, New York.
[38] Williamson, A.R. (1972) Biochem, J. 130, 325.
[38a] Singer, S.J. and Thorpe, N.O. (1968) Proc. Natl. Acad. Sci. U.S. 60, 1371.
[39] Metzger, H. (1970) Ann. Rev. Biochem. 39, 889.
[39a] Metzger, H. (1973) Adv. Immunol. 18, 169.
[40] Holowka, D.A., Strosberg, A.D., Kimball, J.W., Haber, E. and Cathou, R.E. (1972) Proc. Natl. Acad. Sci. U.S. 69, 3399.
[41] Tumerman, L.A., Nezlin, R.S. and Zagyansky, Y.A. (1972) FEBS Letters 19, 290.
[42] Liberti, P.A., Stylos, W.A. and Mauer, P.H. (1972) Biochemistry 11, 3312.
[43] Pilz, I., Kratky, D., Licht, A. and Sela, M. (1973) Biochemistry 12, 4998.
[44] Kabat, E.A. (1966) J. Immunol. 97, 1.
[45] Schechter, B., Schechter, I. and Sela, M. (1970) J. Biol. Chem. 245, 1438.
[46] Goodman, J.W. (1969) Immunochemistry 6, 139.
[47] Haselkorn, D., Friedman, S., Givol, D. and Pecht, I. (1974) Biochemistry, in press.
[48] Oudin, J. (1974). The Antigens (Sela, M., ed.), Vol. 2, Academic Press, New York, in press.
[49] Kunkel, H.G., Mannik, M. and Williams, A.C. (1963) Science 140, 1218.
[50] Hopper, J.E. and Nisonoff, A. (1971) Adv. Immunol. 13, 58.
[51] Oudin, J. and Michel, M. (1963) Compt. Rend. 257, 805.
[52] Wofsy, L., Metzger, H. and Singer, S.J. (1962) Biochemistry 1, 1031.
[53] Singer, S.J. (1967) Adv. Protein Chem. 22,1.
[54] Milstein, C. and Pink, J.R.L. (1970) Progr. Biophys. Mol. Biol. 21, 209.
[55] Wu, T.T. and Kabat, E.A. (1970) J. Exptl. Med. 132, 211.
[55a] Franěk, F. (1970) Developmental Aspects of Antibody Formation and Structure, (Šterzl, J. and Říha, I., eds.), Vol. 1, p. 311, Academia Publishing House of the Czechoslovak Academy of Sciences, Prague.
[56] Goetzl, E.J. and Metzger, H. (1970) Biochemistry 9, 3862.
[57] Franěk, F. (1971) Eur. J. Biochem. 19, 176.
[58] Ray, A. and Cebra, J.J. (1972) Biochemistry 11, 3647.
[59] Haimovich, J., Eisen, H.N., Hurwitz, E. and Givol, D. (1972) Biochemistry 11, 2389.
[60] Weinstein, Y., Wilchek, M. and Givol, D. (1969) Biochem. Biophys. Res. Commun. 35, 694.
[61] Givol, D., Strausbauch, P.H., Hurwitz, E., Wilchek, M., Haimovich, J. and Eisen, H.N. (1971) Biochemistry 10, 3461.
[62] Fleet, G.W.J., Knowles, J.R. and Porter, R.R. (1972) Biochem. J. 128, 499.
[63] Ruoho, A.E., Kiefer, H., Roeder, P.E. and Singer, S.J. (1973) Proc. Natl. Acad. Sci. U.S. 70, 2567.
[64] Nisonoff, A., Wissler, F.C., Lipman, L.N. and Woernley, D.L. (1960) Arch. Biochem. Biophys. 89, 230.
[65] Cahnmann, H.J., Arnon, R. and Sela, M. (1966) J. Biol. Chem. 241, 3247.
[66] Inbar, D., Hochman, J. and Givol. D. (1972) Proc. Natl. Acad. Sci. U.S. 69, 2659.
[67] Heremans, J.F. (1974) The Antigens (Sela, M., ed.), Vol. 2, Academic Press, New York, in press.
[68] Potter, M. (1972) Physiol. Rev. 52, 631.
[69] Wilde, C.E., III and Koshland, M.E. (1973) Biochemistry 12, 3218.
[70] Rowe, D.S. and Fahey, J.L. (1965) J. Exptl. Med. 121, 185.
[71] Spiegelberg, H. (1972) Current Topics in Immunochemistry 1, 165.
[72] Ishizaka, K. (1973) The Antigens (Sela, M., ed.), Vol. 1, p. 479, Academic Press, New York.
[73] Green, N.M. (1969) Adv. Immunol. 11, 1.
[74] Chesebro, B., Bloth, B. and Svehag, S.E. (1968) J. Exptl. Med. 127, 399.
[75] Feinstein, A. and Munn, E.A. (1969) Nature 224, 1307.
[76] Parkhouse, R.M.E., Askonas, B.A. and Dourmashkin, R.P. (1970) Immunology 18, 575.
[77] Green, N.M., Dourmashkin, R.R. and Parkhouse, R.M.E. (1971) J. Mol. Biol. 56, 203.
[78] Valentine, R.C. and Green, N.M. (1967) J. Mol. Biol. 27, 615.
[79] Poljak, R.J., Goldstein, D.J., Humphrey, R.L. and Dintzis, H.M. (1967) Cold Spring Harbor Symp. Quant. Biol. 32, 95.
[80] Sarma, V.R., Silverton, E.W., Davies, D.R. and Terry, W.D. (1971) J. Biol. Chem. 246, 3753.
[81] Schiffer, M., Girling, R.L., Ely, K.R. and Edmundson, A.B. (1973) Biochemistry 12, 4620.
[82] Poljak, R.J., Amzel, L.M., Avey, H.P., Chen, B.L., Phizackerley, R.P. and Saul, F. (1973) Proc. Natl. Acad. Sci. U.S. 70, 3305.
[83] Inbar, D., Rotman, M. and Givol, D. (1971) J. Biol. Chem. 246, 6272.
[84] Padlan, E.A., Segal, D.M., Spande, T.F., Davies, D.R., Rudikoff, S. and Potter, M. (1973) Nature New Biol. 245, 165.
[85] Landsteiner, K. (1945) The Specificity of Serological Reactions, Harvard University Press, Cambridge, Massachusetts.
[86] Pressman, D. and Grossberg, A.L. (1968) The Structural Basis of Antibody Specificity, Benjamin, New York.

[87] Kabat, E.A. (1968) Structural Concepts of Immunology and Immunochemistry, Holt, Rinehart and Winston, New York.
[88] Sela, M. (1966) Adv. Immunol. 5, 29.
[89] Borek, F., ed. (1972) Immunogenicity, North-Holland, Amsterdam.
[90] Crumpton, M.J. (1974) The Antigens (Sela, M., ed.), Vol. 2, Academic Press, New York, in press.
[91] Stollar, B.D. (1973) The Antigens (Sela, M., ed.) Vol. 1, p. 1, Academic Press, New York.
[92] Sela, M., Schechter, B., Schechter, I. and Borek, F. (1967) Cold Spring Harbor Symp. Quant. Biol. 32, 537.
[93] Sela, M. (1969) Science 166, 1365.
[94] Crumpton, M.J. and Wilkinson, J.M. (1965) Biochem. J. 94, 545.
[95] Andres, S.F. and Atassi, M.Z. (1970) Biochemistry 9, 2268.
[96] Fujio, H., Imanishi, M., Nishioka, K. and Amano, T. (1968) Biken's J. 11, 219.
[97] Arnon, R. and Sela, M. (1969) Proc. Natl. Acad. Sci. U.S. 62, 163.
[98] Sachs, D.H., Schechter, A.N., Eastlake, A. and Anfinsen, C.B. (1972) J. Immunol. 109, 1300.
[99] Arnon, R. and Maron, E. (1971) J. Mol. Biol. 61, 225.
[100] Arnon, R. (1973) The Antigens (Sela, M., ed.), Vol. 1, p. 87, Academic Press, New York.
[101] Maurer, P.H. (1964) Progress in Allergy 8, 1.
[102] Gill, III, T.J. (1972) Immunogenicity (Borek, F., ed.), p. 5, North-Holland, Amsterdam.
[103] Sela, M. (1973) The Harvey Lectures, Series 67, p. 213.
[104] De Weck, A.L. (1974) The Antigens (Sela, M., ed.), Vol. 2, Academic Press, New York, in press.
[105] Sela, M. and Mozes, E. (1966) Proc. Natl. Acad. Sci. U.S. 55, 445.
[106] Teitelbaum, D., Arnon, R., Sela, M., Rabinsohn, Y. and Shapiro, D. (1973) Immunochemistry 10, 735.
[107] Haber, E., Page, L.B. and Jacoby, G.A. (1965) Biochemistry 4, 693.
[108] Fischer, J., Spragg, J., Talamo, R.C., Pierce, J.V., Suzuki, K., Austen, K.F. and Haber, E. (1969) Biochemistry 8, 3750.
[109] Cuatrecasas, P., Illiano, G. and Green, I. (1971) Nature New Biol. 230, 60.
[110] Brown, B.L., Ekins, R.P., Ellis, S.M. and Reith, W.S. (1970) Nature 225, 359.
[111] Van Vunakis, H., Wasserman, E. and Levine, L. (1972) J. Pharmacol. Exptl. Therap. 180, 514.
[112] Stylos, W.A. and Rivetz, B. (1972) Prostaglandins 2, 103.
[113] Schechter, I. (1971) Ann. N.Y. Acad. Sci. 190, 394.
[114] Crumpton, M.J. (1966) Biochem. J. 100, 223.
[115] Rotman, M.B. and Celada, F. (1968) Proc. Natl. Acad. Sci. U.S. 60, 660.
[116] Schechter, B., Conway-Jacobs, A. and Sela, M. (1971) Eur. J. Biochem. 20, 321.
[117] Maurer, P.H., Clark, L.G. and Liberti, P.A. (1970) J. Immunol. 105, 567.
[118] Zeiger, A.R. and Maurer, P.H. (1973) Biochemistry 12, 3387.
[119] Teitelbaum, D., Webb, C., Meshorer, A., Arnon, R. and Sela, M. (1973) Eur. J. Immunol. 3, 273.
[120] Webb, C., Teitelbaum, D., Arnon, R. and Sela, M. (1973) Eur. J. Immunol. 3, 279.
[121] Maoz, A., Fuchs, S. and Sela, M. (1973) Biochemistry 9, 4246.
[122] Arnon, R., Maron, E., Sela, M. and Anfinsen, C.B. (1971) Proc. Natl. Acad. Sci. U.S. 68, 1450.
[123] Arnon, R. (1972) Immunity in Viral and Rickettsial Diseases (Kohn, A. and Klingberg, M.A., eds.), p. 209, Plenum Publishing Co., New York.
[124] Lüderitz, O., Westphal, O., Staub, A.M. and Le Minor, L. (1960) Nature 188, 556.
[125] Stellner, K., Lüderitz, O., Westphal, O., Staub, A.M., Leluc, B., Coynault, C. and Le Minor, L. (1972) Ann. Inst. Pasteur 123, 43.
[126] Shier, W.T. (1971) Proc. Natl. Acad. Sci. U.S. 68, 2078.
[127] Shier, W.T. (1973) Nature 244, 99.
[128] Gill, III, T.J. (1971) Current Topics Microbiol. Immunol. 54, 19.
[129] Borek, F. (1968) Current Topics Microbiol. Immunol. 43, 126.
[130] Janeway, Jr., C.A. and Humphrey, J.H. (1969) Israel J. Med. Sci. 5, 185.
[131] Goldman, M. and Leskowitz, S. (1970) J. Immunol. 104, 874.
[132] Gershon, R.K., Maurer, P.H. and Merryman, C.F. (1973) Proc. Natl. Acad. Sci. U.S. 70, 250.
[133] Taussig, M.J. (1973) Current Topics Microbiol. Immunol. 60, 125.
[134] McDevitt, H.O. and Benacerraf, B. (1969) Adv. Immunol. 11, 31.
[135] Mozes, E. and Shearer, G.M. (1972) Current Topics Microbiol. Immunol. 59, 167.
[136] Gowans, J.L. (1965) Brit. Med. Bull. 21, 106.
[137] Gallily, R. and Feldman, M. (1967) Immunology 12, 197.
[138] Unanue, E.R. (1972) Adv. Immunol. 15, 95.
[139] Lipsky, P.E. and Rosenthal, A.S. (1973) J. Exptl. Med. 138, 900.
[140] Jerne, N.K. (1955) Proc. Natl. Acad. Sci. U.S. 41, 849.
[141] Burnet, F.M. (1959) The Clonal Selection Theory of Acquired Immunity, Cambridge University Press, London.
[142] Sell, S. and Gell, P.G.H. (1965) J. Exptl. Med. 122, 423.
[143] Klein, E., Klein, G., Nadkarni, J.W., Nadkarni, J.J., Wigzell, H. and Clifford, P. (1968) Cancer Res. 28, 1300.
[144] Greaves, M.F. and Hogg, N.M. (1971) Progress in Immunology (Amos, B., ed.), p. 111, Academic Press, New York.
[145] Naor, D. and Sulitzeanu, D. (1967) Nature 214, 687.
[146] Byrt, P. and Ada, G.L. (1969) Immunology 17, 503.

[147] Ada, G.L. and Ey, P.L. (1974). The Antigens (Sela, M., ed.), Vol. 3, Academic Press, New York, in press.
[148] Wigzell, H. and Andersson, B. (1969) J. Exptl. Med. 129, 23.
[149] Wofsy, L., Kimura, J. and Truffa-Bachi, P. (1971) J. Immunol. 107, 725.
[150] Rutishauser, U., Millette, C.F. and Edelman, G.M. (1972) Proc. Natl. Acad. Sci. U.S. 69, 1596.
[151] Jerne, N.K. and Nordin, A.A. (1963) Science 140, 405.
[152] Mishell, R.I. and Dutton, R.W. (1967) J. Exptl. Med. 126, 423.
[153] Globerson, A. and Auerbach, R. (1966) J. Exptl. Med. 124, 1001.
[154] Segal, S., Globerson, A., Feldman, M., Haimovich, J. and Sela, M. (1970) J. Exptl. Med. 131, 93.
[155] Green, I., Vassalli, P., Nussenzweig, V. and Benacerraf, B. (1967) J. Exptl. Med. 125, 511.
[156] Gershon, H., Bauminger, S., Sela, M. and Feldman, M. (1968) J. Exptl. Med. 128, 223.
[157] Raff, M.C., Feldmann, M. and De Petris, S. (1973) J. Exptl. Med. 137, 1024.
[158] Miller, J.F.A.P. (1961) Lancet 2, 748.
[159] Good, R.A., Dalmasso, A.P., Martinez, C., Archer, O.K., Pierce, J.C. and Papermaster, B.W. (1962) J. Exptl. Med. 116,773.
[160] Janković, B.D., Waksman, B.H. and Arnason, B.G. (1962) J. Exptl. Med. 116, 159.
[161] Katz, D.H. and Benacerraf, B. (1972) Adv. Immunol. 15, 1.
[162] Claman, H.N., Chaperon, E.A. and Triplett, R.F. (1966) J. Immunol. 97, 828.
[163] Mitchell, G.F. and Miller, J.F.A.P. (1968) J. Exptl. Med. 128, 821.
[164] Sela, M., Mozes, E. and Shearer, G.M. (1972) Proc. Natl. Acad. Sci. U.S. 69, 2696.
[165] Paul, W.E. (1970) Transplant. Rev. 5, 130.
[166] Jerne, N.K. (1967) Cold Spring Harbor Symp. Quant. Biol. 32, 591.
[167] Sela, M. (1967) Gamma Globulins, Nobel Symposium 3 (Killander, J., ed.), p. 455, Almqvist and Wiksell, Stockholm.
[168] Mitchison, N.A. (1967) Cold Spring Harbor Symp. Quant. Biol. 32, 431.
[169] Mitchison, N.A. (1971) Eur. J. Immunol. 1, 18.
[170] Rajewsky, K., Schirrmacher, V., Nase, S. and Jerne, N.K. (1969) J. Exptl. Med. 129, 1131.
[171] Rajewsky, K. (1971) Proc. Roy. Soc. B 176, 385.
[172] Kunin, S., Shearer, G.M., Segal, S., Globerson, A. and Feldman, M. (1971) Cell. Immunol. 2, 229.
[173] Mitchell, G.F. (1974) The Lymphocyte: Structure and Function (Marchalonis, J.J., ed.), Marcel Dekker Inc., New York, in press.
[174] Fuchs, S., Mozes, E., Maoz, A. and Sela, M. (1974) J. Exptl. Med., 139, 148.
[175] Feldman, M. (1973) Nature New Biol. 242, 83.
[176] Waldmann, H. and Munroe, A. (1973) Nature 243, 356.
[177] Tada, T., Okumura, K. and Taniguchi, M. (1973) J. Immunol. 11, 952.
[178] Schimpl. A. and Wecker, E. (1973) J. Exptl. Med. 137, 547.
[179] Trainin, N., Small, M. and Globerson, A. (1969) J. Exptl. Med. 130, 765.
[180] White, A. and Goldstein, A.L. (1972) Immunogenicity (Borek, F., ed.), p. 334, North-Holland, Amsterdam.
[181] Raff, M.C. (1971) Transplant. Rev. 6, 52.
[182] Taylor, R.B., Duffus, W.P.H., Raff, M.C. and de Petris, S. (1971) Nature New Biol. 233, 225.
[183] Roelants, G., Forni, L. and Pernis, B. (1973) J. Exptl. Med. 137, 1060.
[184] Wekerle, H., Cohen, I.R. and Feldman, M. (1973) Nature New Biol. 241, 25.
[185] Smithies, O. and Poulik, M.D. (1972) Science 175, 187.
[186] Peterson, P.A., Cunningham, B.A., Berggård, I. and Edelman, G.M. (1972) Proc. Natl. Acad. Sci. U.S. 69, 1697.
[187] Nakamuro, K., Tanigaki, N. and Pressman, D. (1973) Proc. Natl. Acad. Sci. U.S. 70, 2863.
[187a] Grey, H.M., Kubo, R.T., Colon, S.M., Poulik, M.D., Cresswell, P., Springer, T., Turner, M. and Strominger, J.L. (1973) J. Exptl. Med. 138, 1608.
[188] Bach, M.L., Huang, S.-W., Hong, R. and Poulik, M.D. (1973) Science 182, 1350.
[189] Poulik, M.D., Bernoco, M., Bernoco, D. and Ceppelini, R. (1973) Science 182, 1352.
[190] Askonas, B.A., and Williamson, A.R. (1966) Proc. Roy. B 166, 232.
[191] Shapiro, A.L., Scharff, M.D., Maizel, J.V. and Uhr, J.V. (1966) Proc. Natl. Acad. Sci. U.S. 56, 216.
[192] Melchers, F. and Knopf, P.M. (1967) Cold Spring Harbor Symp. Quant. Biol. 32, 255.
[193] Askonas, B.A. and Parkhouse, R.M.E. (1971) Biochem. J. 123, 629.
[194] Milstein, C., Brownlee, G.G., Harrison, T.M. and Mathews, M.B. (1972) Nature New Biol. 239, 117.
[195] Swan, D., Aviv, H. and Leder, P. (1972) Proc. Natl. Acad. Sci. U.S. 69, 1967.
[196] Mack, B., Faust, C. and Vassalli, P. (1973) Proc. Natl. Acad. Sci. U.S. 70, 451.
[197] Schechter, I. (1973) Proc. Natl. Acad. Sci. U.S. 70, 2256.
[198] Stevenson, R.H. and Williamson, A.R. (1973) Nature New Biol. 245, 101.
[199] Roberts, B.E., Helman, M., Senitzky, N. and Givol, D. (1974) Proc. Natl. Acad. Sci. U.S., in press.
[200] Říhová-Škárová, B and Riha, I. (1972) Current Topics Microbiol. Immunol. 57, 159.
[201] Levine, B.B., Ojeda, A. and Benacerraf, B. (1963) J. Exptl. Med. 118, 953.
[202] McDevitt, H.O. and Sela, M. (1965) J. Exptl. Med. 122, 517.
[203] Mozes, E., McDevitt, H.O., Jaton, J.-C. and Sela, M. (1969) J. Exptl. Med. 130, 1263.

[204] Vaz, N.M. and Levine, B.B. (1970) Science 168, 852.
[205] Cerottini, J.-C. and Unanue, E.R. (1971) J. Immunol. 106, 732.
[206] Maron, E., Scher, H.I., Mozes, E., Arnon, R. and Sela, M. (1973) J. Immunol. 111, 101.
[207] McDevitt, H.O. and Chinitz, A. (1969) Science 163, 1207.
[208] Ellman, L., Green, I., Martin, W.J. and Benacerraf, B. (1970) Proc. Natl. Acad. Sci. U.S. 66, 322.
[209] Benacerraf, B. and McDevitt, H.O. (1972) Science 175, 273.
[210] McDevitt, H.O., Deak, B.D., Shreffler, D.C., Klein, J., Stimpfling, J.H. and Snell, G.D. (1972) J. Exptl. Med. 135, 1259.
[211] Shevach, E.M., Paul, W.E. and Green, I. (1972) J. Exptl. Med. 136, 1207.
[212] Marsh, D.G., Bias, W.B., Hsu, S.H. and Goodfriend, L. (1973) Science 179, 691.
[213] Levine, B.B., Stember, R.H. and Fotino, M. (1972) Science 178, 1201.
[214] McDevitt, H.O. and Landy, M., eds, (1972) Genetic Control of Immune Responsiveness, Academic Press, New York.
[215] Lieberman, R., Paul, W.E., Humphrey, Jr., W. and Stimpfling, J.H. (1972) J. Exptl. Med. 136, 1231.
[216] Mitchell, G.F., Grumet, C. and McDevitt, H.O. (1972) J. Exptl. Med. 135, 126.
[217] Freed, J.H., Bechtol, K.B., Herzenberg, L.A., Herzenberg, L.A. and McDevitt, H.O. (1973) Transplant. Proc. Vol. V, No. 1, p. 167.
[218] Mozes, E. and Shearer, G.M. (1971) J. Exptl. Med. 134, 141.
[219] Shearer, G.M., Mozes, E. and Sela, M. (1972) J. Exptl. Med. 135, 1009.
[220] Mozes, E., Shearer, G.M., Maron, E., Arnon, R. and Sela, M. (1973) J. Immunol. 111, 1429.
[221] Mozes, E. and Sela, M. (1974) Proc. Natl. Sci. U.S., in press.
[222] Rome, E. and Offer, G. (1973) Nature New Biol. 244, 152.
[223] Patrick, J., Lindstrom, J., Culp, B. and McMillan, J. (1973) Natl. Acad. Sci. U.S. 70, 3334.
[224] Berson, S.A. and Yalow, R.S. (1964) The Hormones (Pincus, G., Thimann, K.V. and Astwood, E.B., eds.), Vol. 4, p. 557, Academic Press, New York.
[225] Kirkham, K.E. and Hunter, W.M. (1971) Radioimmunoassay Methods, Churchill Livingstone, London.
[226] Yalow, R.S. and Berson, S.A. (1973) Methods in Investigative and Diagnostic Endocrinology (Yalow, R.S. and Berson, S.A., eds.), North-Holland, Amsterdam, in press.
[227] Mäkelä, O. (1966) Immunology 10, 81.
[228] Haimovich, J. and Sela, M. (1966) J. Immunol. 97, 338.
[229] Sela, M. (1972) Triangle 11, 61.
[230] Engvall, E. and Perlmann, P. (1971) Immunochemistry 8, 871.
[231] Van Weeman, B.K. and Schuurs, A.H.W.M. (1971) FEBS Letters 15, 232.
[232] Avrameas, S. and Guilbert, B. (1972) Biochimie 54, 837.
[232a] Rubenstein, K.E., Schneider, R.S. and Ullman, E.F. (1972) Biochem. Biophys. Res. Commun. 47, 846.
[233] Wide, L., Bennich, H. and Johansson, S.G.O. (1967)
[234] Good, R.A. (1973) The Harvey Lectures, Series 67, p. 1.
[235] Kahar, B.D. and Reisfeld, R.A., eds. (1972) Histocompatibility Antigens, Academic Press, New-York.
[236] Osler, A.G. and Sandberg, A.L. (1973) Prog. Allergy 17, 51.
[237] Mayer, M.M. (1972) Proc. Natl. Acad. Sci. U.S. 69, 2954.